EXHIBIT A

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REVIEW

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Pathophysiological significance of adiponectin

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Abstract Adipose tissue, which classically has been considered as an energy-storing organ, is now viewed as a massive source of bioactive substances such as leptin, tumor necrosis factor (TNF)-α, and adiponectin. Adiponectin was discovered to be the most abundant adipose-specific transcript. Its function had been unclear, but epidemiological and clinical studies have demonstrated that serum levels of adiponectin are inversely associated with body weight, especially abdominal visceral fat accumulation. In addition, adiponectin was inversely related to cardiovascular risk factors, such as insulin resistance, blood pressure, and low-density lipoprotein (LDL) cholesterol and triglyceride levels, and was positively related to high-density lipoprotein (HDL) cholesterol levels. Moreover, low adiponectin concentration is associated with a high incidence of cardiovascular disease (CVD), diabetes, some kinds of cancer, and other various diseases. These associations suggest the clinical significance of adiponectin, and a number of investigations are now being conducted to clarify the biological functions of adiponectin. Recent studies have revealed that adiponectin exhibits antiinflammatory, antiatherogenic, and antidiabetic properties. In addition, adiponectin has been thought to be a key molecule in "metabolic syndrome," which is an epidemiological target for preventing cardiovascular disease. Various functions of adiponectin may possibly serve to prevent and treat obesity-related diseases and CVD. Furthermore, enhancement of adiponectin secretion or action may become a promising therapeutic target.

Key words Adiponectin · Visceral fat · Adipocytokine · Cardiovascular disease · Metabolic syndrome

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Introduction: the discovery of adiponectin

Obesity, in particular, abdominal visceral fat accumulation, is an important risk factor for hyperlipidemia, diabetes mellitus, hypertension, cardiovascular disease (CVD), and some kinds of cancer. However, the molecular mechanism underlying these linkages had not been previously elucidated. We investigated the characteristics of adipose tissue by analyzing the gene expression profile in visceral and subcutaneous fat in the human complementary DNA project.[1] Of approximately 1000 independent clones, 60% of the whole genes were already identified as known human genes. The remaining 40% of genes were novel genes.[2] Although adipose tissue was considered as an energy-storing organ, we found unexpectedly high frequencies of the genes encoding secretory proteins.[3] In subcutaneous adipose tissue, approximately 20% of all known genes were the genes encoding secretory protein (Fig. 1).[2,3] Furthermore, its frequency reached approximately 30% in visceral adipose tissue. In addition, leptin and tumor necrosis factor (TNF)-α had been well recognized as bioactive substances from adipose tissues that regulate the functions of other organs. We named these adipose tissue-derived bioactive substances adipocytokines,[3] although some of them are not cytokines according to the classical category.

We identified the gene that expressed most abundantly and specifically in adipose tissue in 1996.[1] The molecule encoded by this gene, adipose most abundant gene transcript-1 (apM-1), possesses a signal peptide and collagen-like motif (Fig. 2).[1] We termed this matrix-like protein adiponectin. Adiponectin was independently isolated from human plasma as gelatin-binding protein-28.[4] The mouse homologue of adiponectin was cloned as ACRP30 and AdipoQ at the same time.[5,6] However, the significance of this novel molecule was unclear. Then, we developed a method for the measurement of plasma adiponectin levels using an enzyme-linked immunosorbent assay.[7] Measurement of plasma adiponectin revealed the clinical significance of adiponectin.

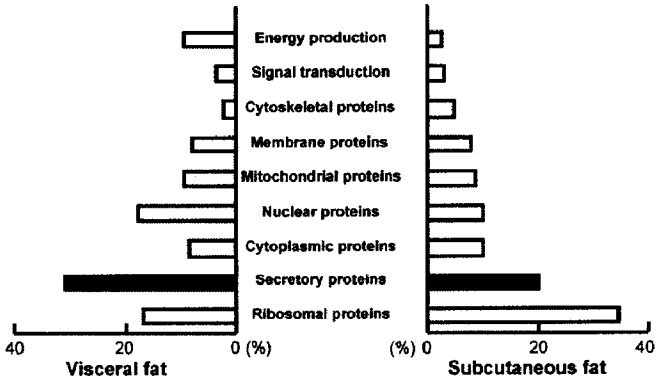

Fig. 1. The high frequency of genes for secretory proteins in adipose tissue. Although adipose tissue has been considered to be an energy-storing organ, an unexpectedly high frequency of the genes encoding secretory proteins is demonstrated. In subcutaneous adipose tissue, approximately 20% of all known genes are the genes encoding secretory protein. Furthermore, its frequency reaches approximately 30% in visceral adipose tissue. [Reproduced with permission from Maeda et al.[2] (1997) Gene 190:227–235; Funahashi et al.[3] (1999) Intern Med 38:202–206]

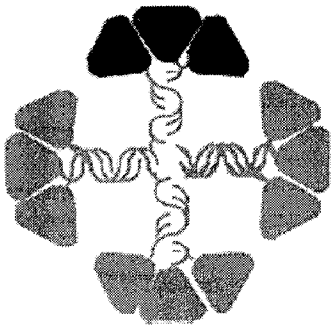

Fig. 2. Structure of adiponectin. This 244-amino-acid protein contains a signal sequence, and a collagen-like domain at the N-terminus and a C1q-like globular domain at the C-terminus. Some units of the trimer of adiponectin are bound in a bouquet-like formation in plasma. [Reproduced with permission from Matsuzawa et al.[106] (2004) Arterioscler Thromb Vasc Biol 24:29–33]

Molecular characteristics of adiponectin

Structure

The gene encoding adiponectin is located on chromosome 3q27, and recent genome-wide scans have mapped a diabetes susceptibility locus to this chromosome.[8–10] This 244-amino-acid protein contains a signal sequence, and a collagen-like domain at the N-terminus and a C1q-like globular domain at the C-terminus (see Fig. 2).[1] The globular domain has sequence homology to collagens VIII and X and complement factor C1q. The crystal structure is similar to that of the TNF family, which has identical folding topologies and similar trimer interfaces.[11] Some units of the trimer of adiponectin are bound up in a bouquet-like formation.[12] Two major oligomeric forms of adiponectin, a hexamer and a 400-kDa high molecular weight (HMW) complex, exist in plasma. The HMW form of adiponectin has been shown to be more active than low molecular weight forms.[13] Hydroxylation and glycosylation of the lysine residues within the collagenous domain of adiponectin are critically involved in regulating the formation of its HMW oligomeric complex.[14]

Full-length adiponectin protein is proteolytically cleaved, with a smaller form, including the globular domain, although in very small amounts.[15] It is reported that the globular domain of adiponectin exhibits more extensive biological activity than the full-length form. However, further studies are needed to clarify the biologically active form of adiponectin and the relative abundance of the different cleavage products in plasma under physiological conditions.

Localization

Adiponectin messenger RNA is exclusively expressed in adipose tissue of humans[1,4] and experimental animals.[5,16] Recent evidence indicated that adiponectin can be produced by organs other than adipose tissue, such as bone marrow,[17] bone-forming cells,[18] fetal tissue,[19] myocytes, cardiomyocytes,[20] and salivary gland epithelial cells,[21] but the major source of plasma adiponectin in adults is the adipocyte. Plasma levels of adiponectin usually range from 3 to 30 μg/ml in adults, whereas adiponectin levels in umbilical venous blood from human fetuses was about 30 μg/ml.[19] Adiponectin was detected in several fetal tissues at mid- and late gestation (from 14 to 36 weeks) but not in the placenta. Adiponectin was detected in human fetal tissues of mesodermic origin, such as brown and white adipocytes, skeletal muscle fibers of diaphragm and iliopsoas, smooth muscle cells of small intestine and arterial walls, perineurium and renal capsule, and tissues of ectodermal origin, such as epidermis and ocular lens. The distribution of adiponectin detection in nonadipose tissues showed a general decline during the progression of gestation.[19] It should be noted that these results do not necessarily demonstrate the production of adiponectin in nonadipose tissues but represent the existence of adiponectin that may adhere to the tissue. In mouse embryos, production of adiponectin was demonstrated in brown adipose tissues (BAT) and surrounding immature tissues using immunohistochemical staining and in situ hybridization.[22] This interspecies difference of fetal localization of adiponectin may be attributed to the small amount of BAT in humans. These studies suggest the adiponectin may have a role during fetal development.

Secretion

Recent studies established the concept that adipose tissue is not only a fuel storage depot but also a critical endocrine tissue secreting a variety of bioactive adipocytokines into the circulation. Despite the importance of adipocytokines in metabolism, the mechanism of secretion from adipocytes remains poorly elucidated. Cellular localization of adiponectin in the steady state is predominantly in the Golgi apparatus or trans-Golgi network (TGN).[23–25] Treatment of 3T3-L1

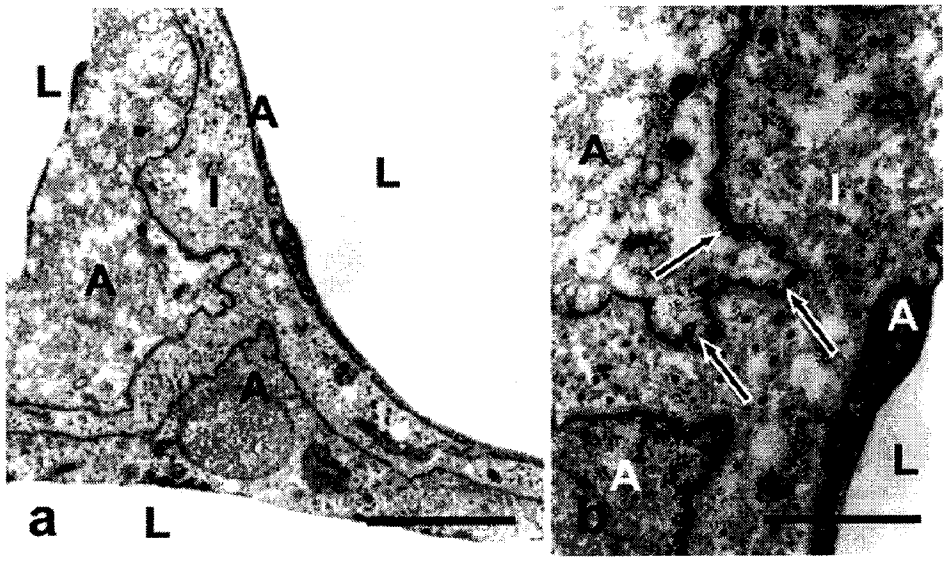

Fig. 3. Caveolae of adipocytes. Three human adipocytes are demonstrated in the *left panel* (a). Many caveolae on the cell membrane (*arrows*) are found at a higher magnification (b). Most studies of function of caveolae have focused on endocytosis and signal transduction. Further morphological studies in adipocytes as secretory cells may reveal a new secretory mechanism of adipocytokines including adiponectin. *A*, adipocytes; *I*, interstitial tissue; *L*, lipid droplet. *Bars* a 2μm; b 1μm

adipocytes with brefeldinA (BFA), an inhibitor of the post-Golgi trafficking pathway, severely inhibited the secretion of adiponectin.[24,25] There should be secretory pathways of adiponectin from Golgi/TGN to the cell surface. Moreover, fractional analyses demonstrated that the adiponectin fraction overlapped with transferrin receptor-positive membranes, indicating that secretory pathways of adiponectin involve the transferrin receptor-positive endosomal system.[25] Generally, some secretory cargo can traffic to the cell surface via the endosomal system.[26,27] The traffic in the endosomal system is controlled by a variety of small molecular weight GTPases of both the Rab and ADP ribosylation factor (Arf) classes.[28–31] Rab11 has been involved in insulin-dependent trafficking in adipocytes.[32] Arf6 controls cell phosphatidylinositol-(4,5)-bisphosphate levels in the plasma membrane and may be involved in regulated exocytosis.[33] In addition, Arf6 may play a role in the recycling of endosomal components with the plasma membrane.[34,35] In 3T3-L1 adipocytes, it has been demonstrated that Rab11 and Arf6 are important mediators of constitutive and insulin-stimulated secretion of adiponectin.[25]

Regulated exocytosis in adipocytes has been investigated by insulin-stimulated secretion of peptides and recycling of vesicles containing GLUT4 to the cell surface.[24] A confocal microscopic study demonstrated that the subcellular distributions of adiponectin and GLUT4 are distinct and non-overlapping,[23] although some molecules have been shown to regulate both adiponectin and GLUT4, implying the existence of common trafficking pathways between adiponectin and GLUT4. One molecule is the GGA1 (for Golgi localizing γ-adaptin ear homology domain ARF-binding protein) protein, which is a monomeric clathrin adaptor that mediates sorting at the TGN of specific cargo in an Arf-dependent manner. Inhibition of GGA1 blocks both traffic of the GLUT4 to its insulin-sensitive intracellular compartment and secretion of adiponectin (but not leptin).[24] It is also speculated that GGA proteins regulate selective cargo formation at the TGN and that insulin may act via a distal (post-TGN) compartment.[24] Another molecule is a kind of v-SNARE. It is suggested that the v-SNARE Vti1a is likely regulating a common and early step in the trafficking of both adiponectin and GLUT4 in 3T3-L1 adipocytes.[36]

There are many caveolae in the cell membrane of adipocytes[37] (Fig. 3). Most studies on the functions of caveolae have focused on endocytosis and signal transduction. Regarding secretion, cholesterol efflux mediated by caveolae or rafts has been investigated. Further morphological studies in adipocytes as secretory cells may reveal a new secretory mechanism of adipocytokines, including adiponectin.

Receptor

Two adiponectin receptors were identified in 2003.[38] AdipoR1 is a receptor for globular adiponectin that is abundantly expressed in skeletal muscle. AdipoR2 is a receptor for full-length adiponectin that is mainly expressed in the liver. Expression of AdipoR1 and -R2 was also detected in the hypothalamus, and increased AdipoR2 expression was found in the paraventricular nucleus (PVN), which may be involved in energy regulation.[39] These molecules are distantly related to the family of seven-transmembrane-spanning G protein-coupled receptors. They have an inverted topology with the N-terminus intracellular and the extracellular portion being small, as distinct from members of this class of receptors that bind peptide hormones.[38,40] Further studies are needed to elucidate the physiological role and the signal transduction pathways of these receptors.

T-cadherin has been demonstrated as a receptor for hexameric and HMW adiponectin but not for trimeric or globular adiponectin.[40] T-cadherin is a glycosylphosphatidylinositol (GPI)-anchored extracellular protein. Tissue distribution of T-cadherin is widespread in cardiovascular system, nervous system, and muscle. T-cadherin is involved in signal transduction in addition to cell–cell ad

hesion.[41,42] However, T-cadherin is not highly expressed in the hepatocyte, which is one of the major targets of adiponectin.[13,43]

The plasma concentration of adiponectin is much higher than that of common cytokines. Therefore, some physiological roles of adiponectin may not be mediated by receptors. Adiponectin may have an important regulatory function that involves low-affinity macromolecular interactions.

Clinical significance of adiponectin

Obesity

Many studies have been showed relationships between plasma adiponectin levels and a variety of diseases. First of all, it was demonstrated that plasma adiponectin levels were inversely correlated with body mass index (BMI).[7] In addition, reduction of body weight increased plasma adiponectin levels.[44] Conversely, leptin is another adipose tissue-specific secretory protein that increased with BMI.[45] The negative correlation between adiponectin levels and visceral adiposity becomes more apparent than that between adiponectin levels and subcutaneous adiposity.[46,47] The mechanism of reduction in plasma adiponectin levels in subjects with visceral fat accumulation has not been elucidated. For one explanation, expression of TNF-α, which is a potent inhibitor of adiponectin promoter activity,[48] increases along with the accumulation of visceral fat.

Cardiovascular disease

The significance of adiponectin is that this protein shows lower levels in patients with ischemic heart disease.[49] In end-stage renal disease, subjects with low adiponectin levels died of cardiac events more frequently during 4 years of observation.[50] These data suggest that hypoadiponectinemia may be a novel and important risk factor of atherosclerosis.[49] Moreover, a prospective study demonstrated that men with high adiponectin levels were at lower risk of myocardial infarction (MI) than those with medium to low levels.[51] This association was independent of traditional cardiovascular risk factors such as hypertension or diabetes.[51] Cross-sectional studies have also demonstrated a relationship between adiponectin levels and CVD.[49,52–54] The risk of CVD was twofold higher in the lowest versus the highest quartiles of adiponectin levels, after adjusting for other risk factors including diabetes, dyslipidemia, hypertension, smoking, and BMI.[49] Low adiponectin levels were also associated with increased carotid atherosclerosis as well as CVD.[53]

Vulnerability of coronary plaque is known to be a very important issue in acute coronary syndrome (ACS). Plasma concentrations of adiponectin in patients with ACS were significantly lower than those in patients with stable angina pectoris. Multiple logistic regression analysis revealed independent correlation of hypoadiponectinemia with the development of ACS.[55] In addition, plasma adiponectin levels are significantly associated with coronary lesion complexity in men with CAD.[56] These data suggest that adiponectin plays a significant role in plaque stability.

Diabetes

Another main clinical significance of adiponectin has been confirmed in diabetes.

We found that subjects with type 2 diabetes had lower adiponectin levels than control subjects.[52] It was also revealed that plasma adiponectin levels were lower in Pima Indians, a unique cohort with a high prevalence of obesity and diabetes.[57] In this cohort, a longitudinal study showed that the individuals with high adiponectin levels were less likely to develop type 2 diabetes than those with low adiponectin levels.[57] Additionally, a high adiponectin level was a more protective factor against development of diabetes than small waist circumference, fasting glucose, 2-h glucose, or fasting insulin levels.[57] Other studies in different populations including the Japanese have also suggested that low adiponectin levels are predictive of future development of insulin resistance and diabetes,[58–61] and that a high adiponectin level is strongly associated with a lower risk of impaired glucose metabolism and type 2 diabetes, particularly in women.[62] In obese and diabetic monkeys, plasma adiponectin levels decreased before the onset of diabetes, in parallel with the decrease of insulin sensitivity.[16] This result supports the findings observed in humans and demonstrates the significance of adiponectin in the development of diabetes.

Hypertension and dyslipidemia

Recent studies have shown the significance of low adiponectin levels in hypertensive patients. A case-control study showed low adiponectin levels in hypertensive patients and a significant negative correlation between plasma adiponectin concentration and mean, systolic, and diastolic blood pressure.[63] Multiple regression analysis also indicated that hypoadiponectinemia was an independent risk factor for hypertension in a study of 758 hypertensive and normotensive men.[64] In addition, a significant relationship between hypertension and adiponectin levels was found in men but not in women.[65] The significance of adiponectin in hypertension has been confirmed in a mouse model. In obese mice, adenovirus-delivered adiponectin significantly decreased blood pressure. This study suggests that hypoadiponectinemia contributes to the development of obesity-related hypertension, at least in part, directly, in addition to its effect via insulin resistance.[66]

It was well documented that adiponectin is associated with dyslipidemia.[46,67–71] Plasma adiponectin levels positively correlated with HDL-C and negatively correlated with triglycerides and apolipoprotein (Apo) B-100 and were not appreciably altered after adjusting for obesity-associated variables.[67] A recent study demonstrated a direct effect of adiponectin in hepatocytes. HMW adiponectin reduced the

hepatic release of ApoB and ApoE, whereas ABCA1 function and ApoA-I secretion were not influenced. In addition, HMW adiponectin reduced hepatic nuclear factor 4-α (HNF4-α) and HNF4-α-regulated genes such as the ApoB gene.[72] This mechanism may explain the association between hyperlipidemia and low adiponectin levels in the portal vein accompanied by visceral fat accumulation.

Metabolic syndrome

Metabolic syndrome is defined by a cluster of pathological conditions that include abdominal obesity, dyslipidemia, hypertension, and hyperglycemia. Metabolic syndrome has been well recognized as a promising target to prevent CVD. Low adiponectin levels have shown an association with the metabolic syndrome in healthy middle-aged subjects.[69] A prospective cohort study in elderly Koreans confirmed the significance of adiponectin.[73] In a study of 661 Japanese adults, the number of components of the metabolic syndrome increased along with the decrease of plasma adiponectin concentration.[74]

We found four types of missense mutation of adiponectin. In these mutations, I164T mutation was accompanied by remarkable hypoadiponectinemia. We have found nine subjects with the I164T mutation; eight of the nine exhibited hypertension or hyperlipidemia and all nine were accompanied by impaired glucose metabolism, including impaired glucose tolerance (IGT) or diabetes mellitus.[75] These results suggest that genetic hypoadiponectinemia may be part of the genetic background of metabolic syndrome. Now, adiponectin is viewed as a key molecule in metabolic syndrome.

Inflammation

It is well established that inflammatory markers are predictive of CVD. Inflammation is now considered as an important pathological basis for both CVD and metabolic syndrome. Some studies found an inverse association between adiponectin and inflammatory markers such as TNF-α, interleukin 6, and C-reactive protein in normal subjects and patients with CVD or metabolic syndrome.[76-80] We found that expression of CRP was detected in adipose tissue and that expression of adiponectin is inversely associated with that of CRP.[77] We also demonstrated that hypertrophied mesenteric adipose tissue produced and secreted adiponectin in Crohn's disease.[81] We think that mesenteric adipocytes may act as immunoregulating cells in the case of intestinal inflammation via adiponectin production. Another study found that synovial fluid and plasma levels of adiponectin were significantly higher in rheumatoid arthritis (RA) than in control subjects. Adiponectin levels were negatively associated with the leukocyte count in RA synovial fluid, implying an antiinflammatory effect of adiponectin in RA synovial fluid.[82] These data indicate that adiponectin may be induced compensatorily in response to local inflammation. Increased adiponectin may prevent fibrosis in these inflammatory lesions.

Cancer and other diseases

Obesity is a significant risk factor for the development of several cancers,[83] but the mechanisms underlying this relationship remain to be fully elucidated. Adiponectin is likely to play an important role in the development and progression of some obesity-related malignancies. Recent studies showed that plasma adiponectin levels are inversely associated with the risk of cancers associated with obesity and insulin resistance.[84] Low adiponectin levels have been associated with endometrial cancer,[85-87] breast cancer, especially in postmenopausal women,[88,89] colorectal cancer,[90,91] gastric cancer,[92] prostate cancer,[93] and leukemia.[94] Low plasma adiponectin levels may be a novel risk factor for cancer. The mechanism of anticarcinogenic effects of adiponectin has been unclear. However, in vitro, recombinant adiponectin potently inhibited endothelial cell proliferation and migration and induced caspase-mediated endothelial cell apoptosis.[95]

Adiponectin will be of note not only in studies of metabolic disorders but also in investigation of various diseases. For example, increasing levels of adiponectin are associated with a decrease in bone mineral density.[96] It finding suggests that adiponectin may play a role in bone metabolism and may prevent osteoporosis.

Biological functions of adiponectin

Antiatherosclerotic effect

We demonstrated that circulating adiponectin can enter into vascular walls. Immunohistochemical examination demonstrated that adiponectin is not present in untreated normal vascular walls of the rat carotid artery. On the other hand, positive immunohistochemical stain was detected in the balloon-injured vascular walls[97] (Fig. 4). In addition, adiponectin has been shown to bind subendothelial collagen, such as collagen V, VIII, and X. We think that endothelial injury in the process of atherogenesis may lead to entry of adiponectin into the subendothelial space, following the binding of adiponectin to these collagens. Adiponectin has beneficial effects on vascular cells including endothelial cells, macrophages, and smooth muscle cells, and may play a protective role against atherogenesis.

Regarding endothelial cells, decreased adiponectin effect enhances endothelial dysfunction.[98] Plasma adiponectin levels were inversely associated with endothelium-dependent vasodilation in both diabetes patients and controls.[99] Nitric oxide (NO), a potent vasodilator, mediates the effect of adiponectin on endothelial cells.[100,101] Adiponectin ameliorates oxidized LDL (oxLDL)-induced suppression of endothelial NO synthase (eNOS) activity. Adiponectin stimulates production of NO through phosphatidylinositol 3-kinase (PI3K)-dependent pathways involving phosphorylation of eNOS by AMP-activated protein kinase (AMPK).[100] Furthermore, endothelium-dependent vasodilation is significantly reduced in adiponectin knockout (KO) mice.[102]

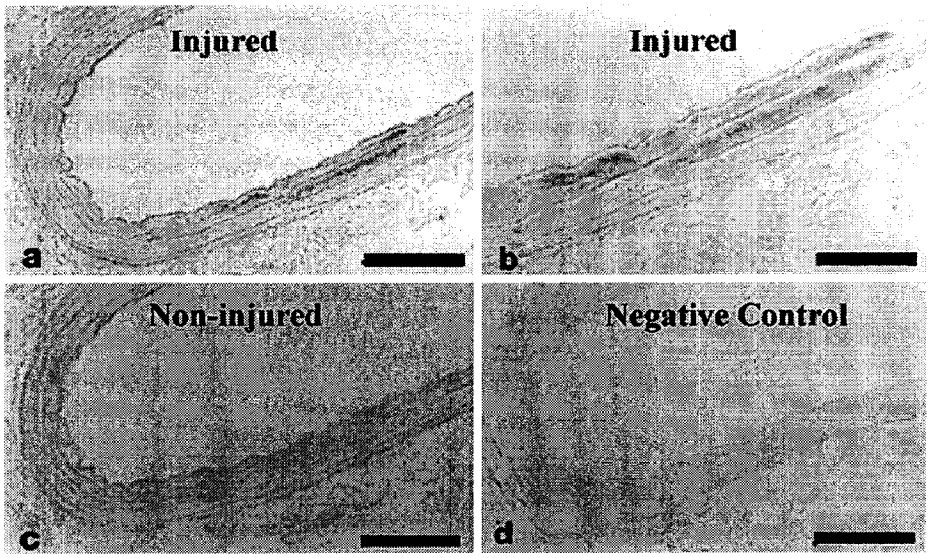

Fig. 4. Localization of adiponectin in an injured artery. Immunohistochemical examination demonstrates the existence of adiponectin in a balloon-injured rat carotid artery (a). At high magnification, adiponectin is detected in subendothelial spaces and media (b). In contrast, adiponectin is not detected in a noninjured artery (c). d Control staining with nonimmune immunoglobulin (Ig). *Bars* a, c, d 100μm; b 50μm. [Reproduced with permission from Okamoto et al.[97] (2000) Horm Metab Res 32:47–50]

Adhesion molecules expressing on the endothelial surface have a critical role in infiltration of macrophages into a vascular wall. The stimulated expression of adhesion molecules by TNF-α was markedly inhibited by the presence of adiponectin dose-dependently.[54] Regulation of adhesion molecules is involved in inflammatory signals, as described next.

In macrophages, adiponectin inhibits the expression of the scavenger receptor class A-1 (SR-A), resulting in markedly decreased uptake of oxLDL and inhibition of foam cell formation.[103] Foam macrophages produce many kinds of matrix metalloproteinases (MMP), which induce rupture of atherosclerotic plaques, causing CVD. Adiponectin increased tissue inhibitor of MMP (TIMP) expression and secretion in human macrophages via induction of IL-10.[104] Consequently, adiponectin may have a role in preventing plaque rupture.

In smooth muscle cells, adiponectin inhibits proliferation and migration. This inhibition was shown to be attributable to binding competition to platelet-derived growth factor (PDGF)-BB receptor of adiponectin and the inhibition of signal transduction through extracellular signal-related kinase (ERK).[105] Adiponectin also inhibited proliferation and migration of smooth muscle cells stimulated by heparin-binding epidermal growth factor (EGF)-like growth factor (HB-EGF). These findings are summarized in Fig. 5. Many offensive factors including oxidized LDL, inflammatory stimuli, and oxidative stress can induce vascular injuries. At that time, circulating adiponectin may accumulate at the injured arteries and protect against the development of atherogenic vascular changes.[106]

Moreover, we investigated platelet thrombus formation in adiponectin KO mice, which showed an accelerated thrombus formation on carotid arterial injury with a He-Ne laser.[107] This study reveals a new role of adiponectin as an endogenous antithrombotic factor. Apart from atherosclerosis, adiponectin may prevent CVD in aspects of cardiac hypertrophy and cardiac ischemic injury. It has been demonstrated in animal models that adiponectin protects against myocardial ischemia-reperfusion injury through both AMPK-dependent antiapoptotic effects and cyclooxygenase (COX)-2-dependent antiinflammatory effects.[108] Adiponectin inhibits hypertrophic signals in the myocardium through activation of AMPK signaling.[109]

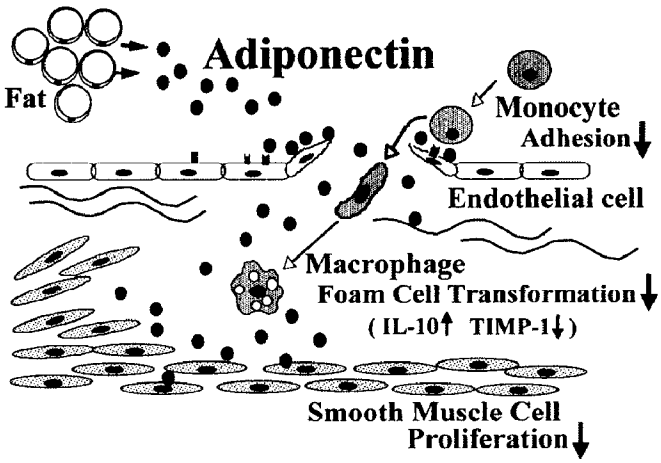

Fig. 5. Antiatherogenic effects of adiponectin. [Reproduced with permission from Matsuzawa et al.[106] (2004) Arterioscler Thromb Vasc Biol 24:29–33]

Antidiabetic effect

In addition to antiatherogenic effects, adiponectin is known as an insulin-sensitizing protein. Intravenous administration of adiponectin lowered hepatic glucose production by reducing the expression of enzymes involved with gluconeogenesis.[110] Treatment with adiponectin, particularly the globular domain of adiponectin, improves insulin sensitivity in animal models of insulin resistance.[43,110–114] Adiponectin is likely to improve insulin sensitivity by stimulating glucose

utilization and fatty acid oxidation through the phosphorylation and activation of AMPK in both skeletal muscle and liver.[111,115] We also demonstrated the antidiabetic effect of adiponectin using adiponectin KO mice. These mice showed no specific phenotype with a normal diet. However, a high-fat and high-sucrose diet induced marked elevation of plasma glucose and plasma insulin levels and marked insulin resistance in these mice.[116] The adiponectin KO mouse may be considered as a model animal of overnutrition-induced diabetes. The supplementation of adiponectin clearly improved this insulin resistance.

As for adiponectin receptors, overexpression of AdipoR1 and -R2 in diabetic mouse liver increased AMPK activation and peroxisome proliferator-activated receptor (PPAR)-α signaling pathway, respectively. AdipoR1- and -R2-deficient mice showed insulin resistance. These data suggest involvement of the adiponectin receptor with insulin resistance in vivo.[117] In vitro, adiponectin binds to the adiponectin receptor on the cell membrane, activating AMPK pathways. Activation of the AMPK signaling pathway reduces serine phosphorylation of IRS proteins, leading to enhanced IRS tyrosine phosphorylation and insulin signaling.[118]

Antiinflammatory effect

Inflammation has been recognized as an important pathological basis in the development of atherosclerosis. Several studies have indicated that adiponectin exhibits antiinflammatory properties in atherogenesis.[76,80,101,119,120] The mechanism of antiinflammatory effects on the endothelial cells has been investigated. Nuclear transcription factor, NF-κB, induces the expression of cytokines and adhesion molecules in the inflammatory process. Adiponectin suppressed TNF-α-induced NF-κB activation without affecting other TNF-α-mediated phosphorylation signals.[120] Moreover, treatment with adenovirus-mediated adiponectin reversed the increased levels of adipose expression of TNF-α and plasma TNF-α in adiponectin KO mice.[116] Besides TNF-α, oxidative stress potently induces inflammatory reactions. Adiponectin also inhibits oxLDL-induced cell proliferation and suppress cellular superoxide generation.[101] A recent study demonstrated that adiponectin promotes the clearance of early apoptotic cells by macrophages through a receptor-dependent pathway involving calreticulin.[121] This function of adiponectin is similar to surfactant proteins and C1q, which serve an antiinflammatory function by promoting the clearance of apoptotic cell debris.[122] In addition, oligomerization of adiponectin seems to be important in the activation of NF-κB signaling pathway.[123]

Adiponectin alters inflammatory reactions in various pathogeneses other than atherogenesis. Adiponectin is protective against chemical-induced colitis in mice, probably because of the inhibition of chemokine production in intestinal epithelial cells and the subsequent inflammatory responses, including infiltration of macrophages and release of proinflammatory cytokines.[124] Adiponectin prevents carbon tetrachloride-induced liver fibrosis by reducing transforming growth factor (TGF) expression in hepatic satellite cells.[125] Adiponectin suppresses TNF-α and induces IL-10 production by Kupffer cells of liver in response to lipopolysaccharide (LPS) stimulation.[126] Continuous infusion of adiponectin attenuates allergic airway inflammation and airway hyperresponsiveness in mice.[127] In bone marrow, adiponectin is an important negative regulator in hematopoiesis and immune systems. Adiponectin blocks fat cell formation in bone marrow cultures by the induction of COX-2 and prostaglandins (PGs) in preadipocytes.[17] A recent study found another mechanism in antiinflammatory effects of adiponectin. Both recombinant and native adiponectin directly bound LPS derived from three different bacteria in the acidic site of inflammation.[128]

Clinical application of adiponectin in the future

Clinical applications of adiponectin have been conducted in animal models for preventing CVD. Adiponectin-deficient mice show excess neointimal thickening in mechanically injured arteries[129,130] (Fig. 6). In adiponectin KO mice, neointimal proliferation is attenuated by adenovirus-mediated adiponectin administration through reducing

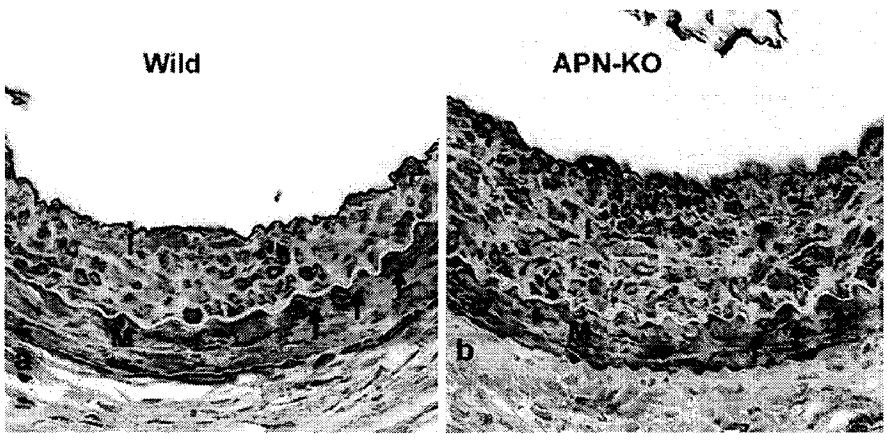

Fig. 6. Adiponectin deficiency exacerbates neointimal thickening after balloon injury. Immunostaining for smooth muscle actin shows neointimal thickening in a femoral artery of a wild-type mouse after mechanical injuries (a). An adiponectin-deficient mouse (*APN-KO*) shows excess neointimal thickening by increase of smooth muscle cells (b). In addition, neointimal thickening in adiponectin-deficient mice is attenuated by adenovirus-mediated adiponectin administration. *Arrows* indicate internal elastic lamina. *I*, intima; *M*, media. [Reproduced with permission from Matsuda et al.[130] (2002) J Biol Chem 277:37487–37491]

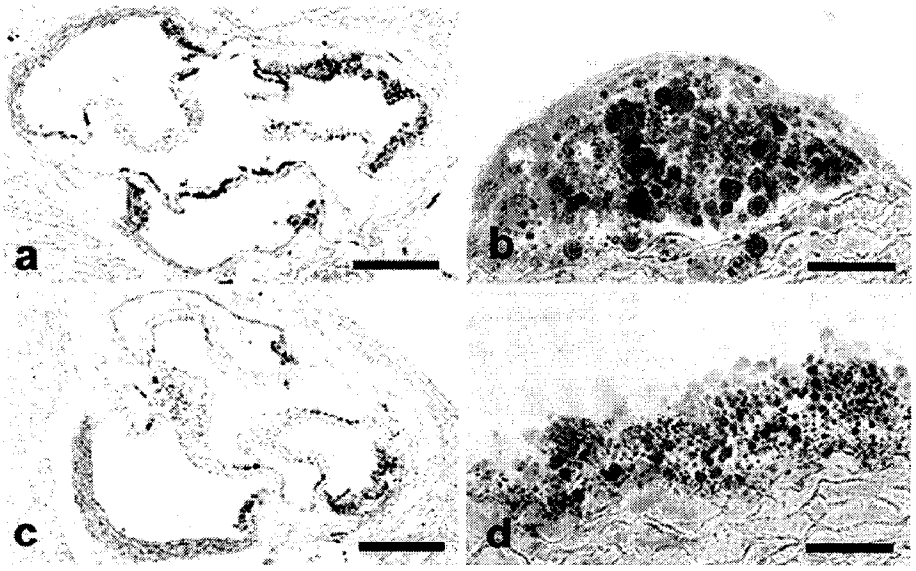

Fig. 7. Adiponectin reduced atherosclerotic plaques of apolipoprotein E-deficient mice. In aortic sinus of an apolipoprotein E-deficient mouse, oil red-O staining shows many atherosclerotic plaques (a). At higher magnification, many large lipid droplets are seen in a plaque (b). Administration of adenovirus-mediated adiponectin in this mouse reduces the area of the plaque in the aortic sinus (c) and the size of the lipid droplets in a plaque (d). *Bars* a, c 500μm; b, d 100μm. [Reproduced with permission from Okamoto et al.[119] (2002) Circulation 106:2767–2770]

proliferation of smooth muscle cells.[130] This result suggests that enhancement of adiponectin may prevent arterial restenosis after balloon angioplasty.[77] Besides smooth muscle cells, foam macrophages are the main components in human atherosclerotic lesions. An apolipoprotein E-deficient mouse is a well-established model of atherosclerosis containing foam cells. We treated these mice with adenovirus-mediated adiponectin. Two weeks after the injection, the plaque area in the aortic sinus was inhibited compared with control mice.[119] The lipid droplets in the lesion of adiponectin-treated mice became smaller compared with nontreated mice (Fig. 7).

Immunohistochemical analyses demonstrated that the adenovirus-mediated adiponectin was localized in the fatty streak lesions. These studies suggest that increase of plasma adiponectin should be a useful target in preventing CVD.

PPARγ-dependent pathways are important targets to induce the expression of adiponectin. PPARγ agonists, the thiazolidinediones, increase plasma adiponectin levels in humans.[48,131–133] Treatment with troglitazone induced plasma adiponectin levels in mildly overweight subjects with glucose intolerance by approximately threefold,[48] and also did so in diabetic patients and in both lean and obese nondiabetic subjects.[131] In a randomized, placebo-controlled study in patients with diabetes, administration of rosiglitazone increased plasma adiponectin levels more than twofold.[132] In addition, pioglitazone increased the ratio of HMW adiponectin/total levels and was related to the hepatic insulin-sensitizing effects.[133] In mice, PPARγ agonists including troglitazone, rosiglitazone, and pioglitazone significantly increased plasma adiponectin levels without affecting body weight.[48] PPARγ agonists induced adiponectin mRNA expression in the adipose tissues of obese mice and enhanced the mRNA expression and secretion of adiponectin in a dose- and time-dependent manner in cultured 3T3-L1 adipocytes.[48] In human and mouse adipose tissue, pioglitazone induces the secretion of HMW adiponectin, but not the secretion of low molecular adiponectin.[134]

As well as PPARγ agonists, the fibrates are also useful to increase adiponectin levels. Significant increase of serum adiponectin was observed in bezafibrate-treated subjects compared with a placebo group.[135] Bezafibrate and fenofibrate significantly elevated adiponectin levels in wild-type mice and 3T3-L1 adipocytes. We also demonstrated that the activation mechanism of adiponectin promoter by fibrates is partly through a PPAR-responsive element (PPRE).[135] In addition, AdipoR2 is induced by both PPARγ and PPARγ in human macrophages.[136]

Analysis of adiponectin promoter is another approach to upregulate the expression of adiponectin. We identified two responsive elements in the human adiponectin promoter region. One is a functional PPAR-responsive element (PPRE), and another is a orphan nuclear receptor, liver receptor homolog-1 (LRH-1)-responsive element (LRH-RE). LRH-1 amplified PPAR-γ-induced transactivation of adiponectin promoter.[137] Our results indicate that PPAR-γ and LRH-1 play significant roles in activation of the adiponectin gene via the PPRE and the LRH-RE in its promoter.

Conclusion

Adiponectin was discovered as an adipose-specific protein. Visceral fat accumulation reduces plasma adiponectin levels. Decreased levels of plasma adiponectin are associated with various kinds of disease. Now, the clinical significance of adiponectin in obesity-related disease has been established. In addition, adiponectin has been shown to have direct effects on obesity-related disease and atherogenesis. Therefore, adiponectin has been recognized as a key molecule in metabolic syndrome.

Various functions of adiponectin provide possibilities to prevent and treat obesity-related diseases and CVD. Furthermore, enhancement of adiponectin secretion or action may become a promising therapeutic target.

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